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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,475	11/25/2003	Svetlana A. Lyapina	CIT1510-5	3177

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EXAMINER

PAK, YONG D

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/723,475	Applicant(s) LYAPINA ET AL.	
	Examiner Yong D. Pak	Art Unit 1652	/

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 November 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 1-10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>8/10/04 & 11/25/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application is a divisional of 10/046,961, now issued as US 6,846,663.

The preliminary amendment filed on November 25, 2003, canceling claims 35-47, has been entered.

Claims 1-34 are pending. Claims 1-10 are withdrawn. Claims 11-34 are under consideration.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-10, drawn to a method of deconjugating a modifier protein from a target protein, classified in class 435, subclass 23.
- II. Claims 11-34, drawn to a method for screening for an agent that affects deconjugation of a modifier protein from a target protein, classified in class 514, subclass 789.

The inventions are distinct, each from the other because of the following reasons:

Inventions I-II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different function or different effects. (MPEP 806.04, 808.01). The instant specification does not disclose that these methods would be used together. The method of deconjugating a modifier protein from a target protein and a method of screening for agents that affect deconjugation of a modifier protein from a target protein are all unrelated as they comprise distinct steps and utilize different products which

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demonstrates that each method has a different mode of operation. Each invention performs this function using structurally and functionally divergent material. Further, the distinct steps require separate and distinct searches. As such, it would be burdensome to search groups I and II together.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Haile on June 21, 2006 a provisional election was made with traverse to prosecute the invention of II, claims 11-34.

Affirmation of this election must be made by applicant in replying to this Office action.

Claims 1-10 are withdrawn from further consideration by the examiner, 37

CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

The information disclosure statement (IDS) submitted on August 10, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The information disclosure statement filed on November 25, 2003 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the IDS filed is a copy from the parent application of the instant application. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or

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specification. It is particularly noted that the sequences in Figures 1-4 lack sequence identification numbers. See particularly 37 CFR 1.821(d).

Specification

Examiner notes that applicants have not updated the relationship of the instant application to its parent application (10/046,961) which has matured into a US patent (U.S. Patent No. 6,846,663). Examiner urges applicants to amend said information by providing the US patent number in response to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 and claims 12-34 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the limitation "a test agent" in line 6. There is insufficient antecedent basis for this limitation in the claim. It is not clear if the "test agent" recited in line 6 is the same as the "agent" recited in line 1. Examiner requests clarification of the phrase.

Claims 11, 13, 16, 18 and 31 and claims 12, 14-15, 17, 19-30 and 32-34 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being

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indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 13, 16, 18 and 31 recite the terms "JAB", "Cul1, Cul2, Cul3, Cul4A, Cul4B, or Cul5", "NEDD8, UBL1, SMT3H2, SMT3H1, APG12, FAT10, Fau, UCRP, URM1, or UBL5", "AMSH, AMSH1 or AMSH2" and "Sic1". The metes and bounds of the terms in the context of the claims are unclear. It appears that applicant may have used it as a short form for names of proteins or compounds. If that is so, reciting the full name would overcome the rejection.

Claims 11 and 27-28 and claims 12-26 and 29-34 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 27-28 recite the phrase "incubating... the target protein". The metes and bounds of the phrase in the context of the above claims are not clear to the Examiner. It is not clear to the protein if a target protein conjugated to a modifier is incubated or if only the target protein is incubated. If only the target protein is incubated, one having ordinary skill in the art can not properly conduct an assay for screening an agent that affect deconjugation of the target protein from its modifier protein. Examiner requests clarification of the above phrase or suggests amending the phrase as "incubating... the modifier protein which is conjugated to the target protein", for example.

Claim 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear to the Examiner as to how those skilled in the art can conclude that the test agent identified by the claimed method is indeed an agent that affect deconjugation of a modifier protein from a target protein and not an which binds to the recited inhibitors, thereby not affecting the assay. This is because in step (a) of the assay, applicants incubate the test agent, target protein, 26S proteasome and inhibitor all together. Applicants have not set up any control steps in which a direct interaction between the inhibitor and the test agent is prevented or if any controls steps are taken into consideration. Therefore, the method lacks essential step(s).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11-34 are drawn to a method of identifying an agent that affect deconjugation of a modifier protein from a target protein by incubating (1) a polypeptide

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having a JAB subunit, such as COP9/signalosome or AMSH proteins, (2) a target protein conjugated to a modifier protein and (3) test agent, wherein in the absence of the test agent, said polypeptide deconjugates the modifier protein from said target protein. These claims encompass a method of using any or all polypeptides having a JAB subunit or any or all COP9/signalosome or AMSH protein and any target proteins with their modifier proteins, including recombinants, mutants and variants thereof. Therefore, these claims are drawn to a method of using a genus of polypeptides having any structure, a genus of target proteins having any structure, a genus of modifier proteins having any structure, including any or all recombinants, mutants or variants thereof. Said genus comprising any or all polypeptides comprising a JAB subunit may or may not cleave any target proteins or those recited in the claims from their modifier proteins. The specification only describes a method of identifying agents that affect deconjugation of specific modifier proteins from specific target proteins, as described in Examples 1-3 of the specification. The few examples found in Examples 1-3 of the specification are not enough to describe the whole genus and there is no evidence on the record of the relationship between the structure of the CSN from *S. pombe* and the structure of any polypeptides comprising a JAB subunit or any CSN or AMSH proteins from any source, including any or all recombinants, mutants and variants thereof. Similarly, there is no evidence on the record of the relationship between the structure of the modifier proteins and their target proteins described in said Examples and the structure of any target proteins and modifier proteins, respectively. Therefore, the specification fails to describe a representative species of the genus comprising any or

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all polypeptides comprising a JAB subunit or any or all CSN or AMSH proteins, genus comprising any or all modifier proteins and genus comprising any or all target proteins, including any or all recombinants, mutants or variants thereof, wherein said genus of polypeptides deconjugates said genus of modifier proteins from said genus of target proteins in the absence of a test agent, that can be used to identify agents that affect deconjugation of said genus of modifier proteins from said genus of target proteins.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 11-34.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 11-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying agents that modulate deconjugation of specific modifier proteins from target proteins, by contacting specific polypeptides comprising a JAB subunit with specific modifier proteins and their target proteins, as described in Examples 1-3 of the specification 2, does not reasonably provide enablement for a method of identifying agents that affect deconjugation using polypeptides comprising a JAB subunit, modifier and target proteins having any structure, including any or all recombinants, mutants or variants thereof. The

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specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 11-34 are drawn to a method of identifying an agent that affect deconjugation of a modifier protein from a target protein by incubating (1) a polypeptide having a JAB subunit, such as COP9/signalosome or AMSH proteins, (2) a target protein conjugated to a modifier protein and (3) test agent, wherein in the absence of the test agent, said polypeptide deconjugates the modifier protein from said target protein. These claims encompass a method of using any or all polypeptides having a JAB subunit or any or all COP9/signalosome or AMSH protein and any target proteins with their modifier proteins, including recombinants, mutants and variants thereof. Said polypeptides comprising a JAB subunit may or may not cleave any target proteins or those recited in the claims from their modifier proteins. Therefore, these claims are drawn to a method of using polypeptides having any structure, target proteins having

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any structure and modifier proteins having any structure, including any or all recombinants, mutants or variants thereof.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of any or all polypeptides having a JAB subunit or any or all COP9/signalosome or AMSH protein, any or all target and modifier proteins broadly encompassed in the claimed method, wherein said polypeptides having a JAB subunit or any or all COP9/signalosome or AMSH protein may or may not cleave said target proteins from said modifier proteins. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

However, in this case the disclosure is limited to The specification only describes a method of identifying agents that affect deconjugation of specific modifier proteins from specific target proteins, as described in Examples 1-3 of the specification, but provides no guidance with regard to a method of identifying agents that affect deconjugation of any or all target proteins from any or all modifier proteins. It would require undue experimentation of the skilled artisan to make and use the agents in the claimed method. In view of the great breadth of the claim, amount of experimentation required to identify and make the polypeptides, amount of experimentation required to

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identify polypeptides comprising a JAB subunit that cleaves any or all modifier protein from any or all target protein, the lack of guidance, working examples, and/or unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the proteins to identify agents that affect deconjugation of any or all modifier proteins from their target proteins.

While enzyme isolation techniques, recombinant and mutagenesis techniques and other related techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications in a polypeptide as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method of screening for agents that affect deconjugation of a target protein from a modifier protein by using any or all polypeptides having a JAB subunit or any or all COP9/signalosome or AMSH protein and any or all target and modifier proteins, because the specification does not establish: (A) a universal method to identify agents that affect deconjugation of any or all modifier proteins from any or all target proteins by contacting a said polypeptide with any or all modifier and target proteins; (B)

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regions of said polypeptide which may be modified without affecting its ability to deconjugate a modifier protein from its target protein; (C) the general tolerance of said polypeptide to modification and extent of such tolerance; (D) a rational and predictable scheme for selecting polypeptides having a JAB subunit or any or all COP9/signalosome or AMSH protein, target and modifier proteins with an expectation of said polypeptide cleaving said target protein from said modifier protein; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of screening for agents that affect deconjugation of a target protein from a modifier protein by using any or all polypeptides having a JAB subunit or any or all COP9/signalosome or AMSH protein and any or all modifier and target proteins. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides comprising a JAB subunit, modifier and target proteins having the desired biological characteristics used in the method and polypeptides that cleave a modifier protein from a target protein is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 32-33, 36-37, 41-57 and 74-75 and 77-78 of copending Application 10/047,253 and claims 37-40, 42-46, 48-66 and 87-88 of copending Application 10/340,578. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are claiming common subject matter, as follows: Claims 11-34 of the instant application and claims 32-33, 36-37, 41-57 and 74-75 and 77-78 of 10/047,253 and claims 37-40, 42-46, 48-66 and 87-88 of 10/340,578 are all directed to a method of determining amount of deconjugation of a modifier protein from its target protein in order to screen or identify agents that affect deconjugation of said modifier protein from said target protein or agents that affect isopeptidase activity. The method of the instant application and the method of the referenced applications are the same because identification of an agent that affect isopeptidase activity of a polypeptide that deconjugates a modifier protein

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from its target protein is also an agent that affects deconjugation of a modifier protein from its target protein, since the ability of the polypeptide to deconjugate is affected.

Therefore, the conflicting claims are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

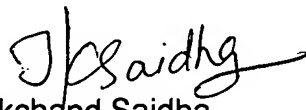
None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652


Tekchand Saidha
Primary Patent Examiner 1652